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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/936,449	12/20/2001	Monica G. Marcu	213373	4132

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EXAMINER	
WORTMAN, DONNA C	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 02/10/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/936,449	MARCU ET AL.	
	Examiner	Art Unit	
	Donna C. Wortman, Ph.D.	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *18-21 and 23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-23* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *of 1/17/02* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Applicant's election with traverse of the claims of species (I) and of species (A) in the response filed 3 November 2003 is acknowledged. The traversal is on the ground(s) that all of the pending claims are directed to the use of coumarin or a derivative thereof to bind to a chaperone protein, whereupon the binding of the chaperone protein to its client polypeptide is inhibited, that the common structural feature is the ability to bind to a coumarin derivative, and that a common utility is the inhibition of cellular proliferation. This is not found entirely persuasive because claims 16-21 and claim 23 do not share the utility of inhibition of cellular proliferation with the remaining claims. However, on further consideration, claims 1-15 and 22 are seen to share the common technical feature of binding coumarin or a derivative thereof to a chaperone protein, whereupon the binding of the chaperone protein to its client polypeptide is inhibited, with the effect that cellular proliferation is inhibited. Claims 16 and 17 are also rejoined as the subject matter can be examined without additional burden on the Office.

The remaining requirement is still deemed proper and is therefore made FINAL.

Claims 1-17 and 22 have been rejoined and are under examination. Claims 18-21 and 23 are withdrawn from consideration as drawn to non-elected inventions.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-6, 8-15, and 22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for contacting the chaperone protein Hsp90 with coumarin or a coumarin derivative so that the coumarin or coumarin derivative inhibits Hsp90 from binding a client protein, does not reasonably provide enablement for binding a coumarin or coumarin derivative with any other chaperone protein so as to inhibit the chaperone protein from binding a client protein. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification lists a variety of chaperone proteins, including Hsp90, that are known in the art, but does not teach that any or all such proteins, other than Hsp90, actually bind coumarin or coumarin derivatives in such a way as to inhibit the chaperone proteins from binding the client proteins. In this regard, Jolly et al. (Journal of the National Cancer Institute 92:1564-1572, 2000) is cited. Jolly et al. (not prior art) is a review article published after the filing date of provisional 60/124135 whose benefit is claimed under 119(e) in the instant application, and is cited to reflect the state of the art at or about the time the instant invention was made. Jolly et al. list a variety of different heat shock proteins that act as molecular chaperones, with different client proteins, in many different organisms (see, e.g., Table 1). Even those chaperones that are thought to have a role in oncogenesis are not disclosed as having structural features in common, and do not interact with the same array of client proteins (see, e.g., page 1566-1568 and Fig. 1). Hsp90 is the only chaperone protein that is identified in the instant application as binding

coumarin or a coumarin derivative so as to inhibit binding of the chaperone to a client protein, and there is no teaching as to how to identify others that would have the required properties. Taking into account the state of the art at the time the invention was made, and the amount of guidance provided by applicant as to which other chaperone proteins would work in the claimed invention, one of skill in the art at the time the invention was made would not be able to practice the invention throughout the claimed scope without undue experimentation.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 8-15 and 22 are rejected under 35 U.S.C. 102(b) as anticipated by US Patent 5,096,887 to Casley-Smith, which discloses use of coumarin and coumarin derivatives, administered by various routes, including topically, to treat edema, to increase proteolysis, and to treat various conditions including malignancies. See, e.g., col. 2, lines 27-30; col. 3, lines 1-28; col. 3, line 66-col. 4, line 3. While Casley-Smith does not disclose that coumarin and its derivatives bind Hsp90, Hsp90 is constitutively expressed in cells and is

overexpressed in tumor cells, and the binding of coumarin and similar drugs to Hsp90 necessarily occurs when the drug is administered. Consequently, Casley-Smith is deemed to anticipate the claimed subject matter because of the inherent binding properties of coumarin for Hsp90 and of Hsp90 for its client proteins.

Claims 1-7, 16, 17, and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Civitico et al. (Journal of Medical Virology 31:90-97, 1990), cited on PTO 892. Civitico et al. disclose the treatment of duck hepatitis B virus-infected cells with a variety of antiviral compounds, including coumermycin A1 and novobiocin, with the subsequent inhibition of hepatitis B virus, anticipating the subject matter of claims 1-7, 16, 17, and 22. See Table 1, e.g. While Civitico et al. do not disclose the participation of Hsp90 in the mechanism of action of coumermycin A1 and novobiocin, Hsp90 is constitutively expressed in cells, the binding of coumermycin A1 and novobiocin to Hsp90 necessarily occurs when the drug is administered to the cells.

Claims 1-3, 5-15, and 22 are rejected under 35 U.S.C. 102(b) as anticipated by Kennedy et al. (Journal of Clinical Oncology 13(5):1136-1143, 1995), cited on PTO 892. Kennedy et al. disclose the use of novobiocin, 4 g/day, in the treatment of metastatic breast cancer, which results in the inhibition of cellular proliferation of both normal and cancer cells. While Kennedy does not disclose that novobiocin inhibits cell growth because it binds Hsp90, Hsp90 is constitutively expressed in normal cells and overexpressed in tumor cells, and the binding of novobiocin to Hsp90 necessarily occurs when the drug is administered. Consequently, Kennedy is deemed to anticipate the claimed

subject matter because of the inherent binding properties of novobiocin for Hsp90 and of Hsp90 for its client proteins, and because Kennedy's treatment results in inhibition of cell proliferation.

Claims 1, 3, 5-10, 12-14, and 22 are rejected under 35 U.S.C. 102(e) as anticipated by US Patent 6,037,326 to Styczynski et al. which was filed 31 December 1996, cited on PTO 892. The claims are drawn to a method of inhibiting binding of a chaperone protein with its client protein or client polypeptide, comprising contacting a chaperone protein with coumarin or a coumarin derivative, such that the coumarin or coumarin derivative binds the chaperone protein, and, when the contacting is done *in vivo*, results in the inhibition of cell proliferation. The claims encompass any *in vivo* treatment with novobiocin or other coumarin or coumarin derivative that results in the binding of the coumarin or coumarin derivative to a chaperone protein and subsequent inhibition of cellular proliferation. Styczynski et al. disclose topical administration of coumarins, including novobiocin, to reduce hair growth. While Styczynski teaches that novobiocin and other coumarins inhibit hair growth because they bind to DNA topoisomerases within skin cells and inhibit hair follicles, since Hsp90 is constitutively expressed in mammalian cells, and since Hsp90 client proteins are normally present in cells, the binding of coumarins including novobiocin to Hsp90 also necessarily occurs when these drugs are administered *in vivo*, and Styczynski is deemed to anticipate the claimed subject matter because of the inherent binding properties of coumarin and coumarin derivatives

for Hsp90, and because Styczynski's treatment results in inhibition of cell proliferation.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Donna C. Wortman, Ph.D. whose telephone number is 571-272-0913. The examiner can normally be reached on Monday-Thursday, 7:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on 571-272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Donna C. Wortman, Ph.D.
Primary Examiner
Art Unit 1648

dcw